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Topiramate for intractable childhood epilepsy*

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To better define the efficacy and tolerability of the new anticonvulsant topiramate in pediatric patients, the clinical courses of 49 children with intractable seizures were monitored during topiramate therapy. The 80% of children who had complex partial seizures experienced better seizure control with topiramate than the 20% who had generalized seizures. Efficacy was greatest with doses between 2.5 and 7.5 mg/kg/day. More than half the children on topiramate experienced adverse effects which could interfere with learning at school, but 20% demonstrated increased alertness or improved behavior. Topiramate is effective and may be considered as part of the treatment pathway for complex partial seizures in children, although careful monitoring of cognitive function is required.

Key words: topiramate; antiepileptic drug; epilepsy; children.

INTRODUCTION

Topiramate (TPM) is a new antiepileptic drug that acts through blocking of sodium channels, enhancing GABA-induced influx of chloride, and inhibiting kainate/AMPA glutamate receptors[1]. Although the usefulness of TPM has been clearly demonstrated in adults, less information is available concerning the efficacy and tolerability of TPM in children. We reviewed the clinical course of all patients with intractable seizures in our university-based Pediatric Neurology Clinic, who were started on TPM after the drug was approved for use in the USA.

MATERIALS AND METHODS

The effects of TPM were studied in all children who were started on TPM between February 1997 and September 1997. Patients were divided into two groups based on seizure type: children with complex partial epilepsy and children with generalized epilepsy. Medical records were reviewed at 1, 3 and 6 months following start of therapy for seizure type, seizure frequency, side effects, TPM dose and concurrent medication. A scale of measuring improvement in seizures was adopted: 4 represented a 100% reduction in seizure frequency, 3 represented a $<75\%$ reduction, 2 represented a $>50\%$ improvement, 1 represented a $<50\%$ improvement, 0 represented no change, and -1 represented an increase in seizure frequency.

RESULTS

A total of 49 children were studied, including 23 boys and 26 girls, who ranged in age from 1.5 to 19 years (mean 9.8 years). Children with complex partial epilepsy constituted 80% of the group, and patients with generalized epilepsy constituted 20%. Three patients with Lennox–Gastaut syndrome were included in the group with generalized epilepsy. Most children, whether they had partial or generalized seizures, had received five or six antiepileptic drugs before being started on TPM. Of the 49 patients, 13 received TPM as monotherapy and 36 received TPM as adjunctive therapy. At the end of 1 month, 44 patients remained on TPM. The number of patients available for review at 3 months was 41, and at 6 months was 34. This decrease was caused by patients who were started on TPM later and received medication for less than 3 or 6 months, as well as by patients who were taken off TPM for inefficacy or adverse effects.

In our study TPM proved more effective in controlling partial seizures than in controlling generalized seizures (Table 1). Furthermore, among patients with generalized seizures, TPM appeared more effective

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Table 1: Efficacy by seizure type: seizure improvement scale (-1 to $+4$).

	1 month	3 months	6 months
Complex partial seizures	1.5 ($n = 36$)	2.2 ($n = 34$)	2.0 ($n = 28$)
Generalized seizures	1.8 ($n = 8$)	1.0 ($n = 7$)	1.0 ($n = 6$)

Table 2: Efficacy of multiple AEDs: seizure improvement scale (-1 to $+4$).

	1 month	3 months	6 months
Gabapentin	3.0 ($n = 2$)	4.0 ($n = 2$)	4.0 ($n = 1$)
Carbamazepine	2.6 ($n = 5$)	2.2 ($n = 5$)	2.4 ($n = 5$)
Felbamate	0.8 ($n = 4$)	3.0 ($n = 3$)	2.3 ($n = 3$)
Valproate	1.6 ($n = 9$)	1.7 ($n = 9$)	2.0 ($n = 7$)
Lamotrigine	-0.3 ($n = 4$)	2.0 ($n = 4$)	1.5 ($n = 2$)
TPM alone	1.7 ($n = 13$)	2.0 ($n = 11$)	1.2 ($n = 9$)

Table 3: Efficacy and dose: seizure improvement scale (-1 to $+4$).

	1 month	3 months	6 months
$<$2.5mg/kg/d	1.7 ($n = 3$)	2.3 ($n = 3$)	1.3 ($n = 3$)
$2.5 - 5.0$ mg/kg/d	2.2 ($n = 9$)	2.3 ($n = 9$)	2.8 ($n = 8$)
$5.0 - 7.5$ mg/kg/d	1.3 ($n = 12$)	2.6 ($n = 10$)	2.1 ($n = 7$)
$7.5 - 10$ mg/kg/d	1.8 ($n = 6$)	2.2 ($n = 6$)	1.0 ($n = 6$)
$>$10 mg/kg/d	0.5 ($n = 4$)	1.0 ($n = 4$)	0.5 ($n = 4$)

Table 4: Adverse effects of topiramate.

	Number of patients	Percent of patients
Decreased appetite	14	28
Decreased cognition	11	22
Decreased speech	8	16
Decreased energy	7	16
Worsened behavior	7	14
Increased sleepiness	7	14
Increased appetite	4	8
New-onset drooling	3	6
Decreased sleep	3	6

in controlling seizures at 1 month than at 6 months. Among patients with complex partial epilepsy, we reviewed the efficacy of TPM as monotherapy and as adjunctive therapy. Findings are summarized in Table 2, with drugs listed in order of decreasing efficacy at 6 months. While results suggest that the combination of TPM with gabapentin, carbamazepine, or felbamate is particularly effective, the numbers are small and not clinically significant.

TPM doses were escalated at a rate of 25 to 50 mg per week. To determine if there were variations in efficacy because of dose, we evaluated efficacy as a function of dose among the 34 children with complex partial epilepsy. Results indicate that efficacy was greatest with doses between 2.5 and 7.5 mg/kg/day (Table 3). At lower doses, between 2.5 and 5.0 mg/kg/day, efficacy appeared to increase over time, while at higher doses, between 7.5 and 10.0 mg/kg/day, efficacy appeared to decrease over time.

Table 5: Beneficial effects of topiramate.

	Number of patients	Percent of patients
Increased alertness	8	16
Improved behavior	4	8

Adverse effects reported during treatment with TPM were monitored (Table 4). Although decreased appetite was the most commonly reported single effect, a constellation of effects reflecting increased psychomotor dysfunction were far more significant. Of the 49 patients, 53% had problems with one or more of the following:

- decreased cognition,
- decreased speech,
- decreased energy,
- worsened behavior.

Beneficial effects were reported in some patients (Table 5). Of the 49 patients, 20% reported improvement in one or both of the following:

- increased alertness,
- improved behavior.

Among these 10 children, the mean seizure improvement scores were 1.3, 1.4, and 1.4 at 1, 3 and 6 months, respectively. Among patients in the entire cohort, 31% reported beneficial effects or no adverse effects.

DISCUSSION

Topiramate is a monosaccharide derivative of the naturally occurring *d*-fructose with a sulfamate substitution. It is thought to have a broad range of antiepileptic activity that functions primarily to prevent seizure spread rather than raise seizure threshold. Its three postulated mechanisms include modulating voltage-dependent sodium conductance, potentiating inhibitory GABA-evoked currents, and blocking the kainate/AMPA subtype of the excitatory glutamate receptor. TPM also inhibits some carbonic anhydrase isoenzymes; however, its effect is generally much weaker than that of acetazolamide.

Findings in our study indicate that TPM is an effective anticonvulsant medication in children, particularly for those with intractable complex partial seizures. Among the children with partial seizures who were reviewed after 3 months and after 6 months, half experienced a greater than 50% reduction in seizure frequency. The response among the children with generalized seizures was less encouraging. Our findings are concordant with those from a single-center open-label trial of TPM monotherapy substitution in five pediatric patients with complex partial epilepsy, which

emphasized that TPM monotherapy may be effective if dose titrations of TPM and the concomitant antiepileptic drug are undertaken carefully[2]. Our findings, however, are somewhat different than those from a multi-center open-label study of adjunctive TPM therapy in 18 children with Lennox–Gastaut syndrome, in which 75% of patients reported a greater than 50% decrease in the total number of seizures[2]. The results of two large, double-blind, placebo-controlled trials of adjunctive TPM therapy in children with refractory partial-onset seizures and with Lennox–Gastaut syndrome are pending[2].

The minimal effective dose of TPM as adjunctive therapy is approximately 200 mg/day[3]. In two recent multi-center adult studies of adjunctive TPM therapy, maximal seizure reduction rates were seen in patients taking between 400 and 1000 mg/day of TPM[4, 5]. In our study, maximal efficacy was seen at doses between 2.5 and 7.5 mg/kg/day. Also, efficacy at the lower range of these doses (2.5 to 5.0 mg/kg/day) was observed to remain steady and, in several cases, increase over time.

In our study, a significant percentage of adverse effects attributed to TPM were CNS-related. These included decreased cognition, somnolence, decreased speech, and worsened behavior. Over half of the patients in our study experienced one or more of these side effects, any of which could adversely affect learning at a critical age. However, because adverse effects that could interfere with learning may be subtle and develop insidiously, the use of objective measures to monitor changes in cognition may be beneficial. While there is evidence that many of the CNS-related side effects may dissipate or disappear completely over time[1], we did not continue patients on TPM for the duration of the study if they experienced unacceptable adverse effects. It is important to note that TPM does not uniformly produce adverse CNS effects. Twenty percent of children in our study experienced increased alertness and/or improved behavior. Finally, decreased appetite with subsequent weight loss was a common adverse effect in our study, affecting 28% of patients. This is consistent with other findings that weight loss may be one of the more common effects[3, 4].

We conclude that TPM is significantly effective in improving seizure control in children and may be considered as part of the treatment pathway for those with complex partial seizures. Although several new antiepileptic drugs have been introduced in this decade, none have proven to be entirely safe or effective. While further studies continue, TPM at present may be the safest and most effective new drug in the treatment of pediatric epilepsy. However, careful monitoring of cognitive function will be required in pediatric patients.

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